REMARKS

The office action of July 10, 2007 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is requested. Claims 22-25, 28-30, and 35-47 remain in this case, claims 45-47 being added and 22-25, 29-30, 35-36, 43 and 44 being amended by the present response. No new matter has been added. Specifically, claims 45-47 are fully supported by page 3, lines 6-20 of the application, as filed. The amendments to claims 25, 43 and 44 are fully supported by the Abstract, page 2, line 30 to page 3, line 5 and page 5, lines 7-8 of the application, as filed. The amendments to claims 22-24, 29-30 and 35-36 were made to correct dependencies from the amended claims.

STATEMENT OF THE SUBSTANCE OF THE INTERVIEW

The Applicant's attorney, Meghan Van Leeuwen, Bernhard Muellinger, an inventor of the present invention, and William Zimlich, a representative of the assignee, attended an in-person interview with the Examiner, Glenn Dawson, on November 30, 2007.

The Applicant demonstrated the device used in a method of the present invention during the interview.

Claim 25 was discussed in the interview. Goodman, Gilmore, and Rapaport, prior art of record, were discussed during the interview.

The parties first discussed the specification and 112 rejections. The Applicant's attorney and the Examiner agreed that replacing "breathing parameters" with "tidal volume or respiratory flow" would overcome these rejections.

The parties then discussed the Goodman reference. The Applicant's attorney pointed out that Goodman does not teach or suggest adjusting the respiratory flow or tidal volume. The Examiner stated that he needed to review Goodman in detail to determine whether or not this statement was correct.

The parties then discussed Gilmore. The Applicant's attorney stated that Gilmore does not teach or suggest adjusting aerosol doses. At this point, the parties also discussed the particular language of claim 25.

The Examiner stated that he had intended to reject the independent claims over the combination of Gilmore and Goodman in the office action. The Applicant's attorney stated that this combination still does not teach or suggest claim 25. The Examiner suggested that the Applicant explain in writing why the combination of Gilmore and Goodman would not teach or suggest the current claims. No agreement was reached with respect to the allowability of claim 25.

Applicant believes that this statement satisfies the requirements to file a Statement of the Substance of the Interview, and accurately represents the substance of the interview conducted.

Rejection under 35 U.S.C. §102

Claims 22, 25, 28-32, and 35,36-39 and 42-44 were rejected under 35 U.S.C. 102(b) as being anticipated by Goodman (5,813,397). Applicant respectfully disagrees with the rejection.

As amended, independent claim 25 claims, in part, "adjusting a respiratory flow or a tidal volume of the inhalation device based on the inhalation parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation". Claims 43 and 44 similarly claim "adjusting a respiratory flow or a tidal volume of the inhalation device based on the individual patient parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation" and "adjusting a respiratory flow or a tidal volume of the inhalation device based on the aerosol parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation", respectively.

The Examiner states that Goodman "has the capability to detect changes ... including flow rate and tidal volumes and adjust these parameters" (page 3, lines 1-3, present office action, dated July 10, 2007) but does not indicate where this is disclosed in the patent. Goodman does not disclose <u>adjusting</u> flow rate or tidal volume using individual patient parameters or aerosol parameters.

Tidal volume is the volume of air inhaled and exhaled with each breath. Tidal volume and respiratory flow both relate to air entering and leaving a patient's lungs during a breath. Goodman discloses that "the selected particle size can then be used with an optimal inspiratory flow, inspiratory pause, expiratory flow, and tidal volume to deliver the aerosol medication to the most therapeutically efficacious locations in the patient's airway" (column 34, lines 41-45). Goodman discloses adjusting aerosol delivery based on inspiratory flow, pause, expiratory flow, and tidal volume. Goodman further discloses: "It is another object of the invention to deliver aerosolized compounds in response to a measure of a patient's breathing pattern during inspiration. It is another object to select the optimal point or points for release of one or more pulses of medication based on an analysis of the patient's inspiratory flow in a first detected flow and to release the medication on the occurrence of the determined point or points during a subsequently detected inspiratory breath" (column 5, lines 17-24). Goodman "monitor[s] the patient's breath flow patterns…." (column 12, line 48). Goodman also states that it is "capable of autonomously modifying the initial therapy program based on detected progressive changes in the patient's breath flow and corresponding pulmonary functions." (column 6, lines 26-29).Goodman discloses only measuring, analyzing, and detecting respiratory flow and adjusting aerosol delivering based on measured respiratory flow. Goodman does not disclose adjusting respiratory flow or tidal volume and does not disclose adjusting respiratory flow or tidal volume based on individual patient parameters for the patient or aerosol parameters.

Goodman is merely a variable dose inhaler. It still provides a metered dose; the amount of medication in that particular dose just varies from patient to patient. The Applicant has reviewed the cites from Goodman made by the Examiner on page 4, lines 2-7 of the present office action, and finds no disclosure of adjusting the tidal volume or respiratory flow in Goodman. Note that some of these passages discuss trying to get the patient to adjust their breathing (for example, see column 5, lines 9-10, "feedback for prompting the patient to obtain a suitable breathing pattern for delivering a selected medication…"); however, claims 25, 43 and 44 of the present application adjust a respiratory flow or tidal volume of the inhalation device. Goodman does not disclose a method or device that is capable of adjusting a respiratory flow or tidal volume of an inhalation device.

By adjusting the respiratory flow or tidal volume of the inhalation device, the method of the present invention is able to optimize the dose of the active ingredient of an aerosol that is applied to a desired section of a lung of a patient, as claimed in claims 25, 43 and 44. Goodman does not disclose an optimal dose of at least one active ingredient of at least one aerosol being applied to a desired section of a lung of the patient during the controlled inhalation. As the attached Brand paper explains (filed as part of an IDS dated July 11, 2006), it is very difficult to optimize dosage of an active ingredient for an aerosol from patient to patient without controlling the breathing pattern of the patient. "The study has shown that within the study population the inhaled air volume and flow rate were quite different. Consequently, **total particle deposition varied between 20 and 95%, depending on breathing patterns**." (Brand, 1999, Abstract, page 724). "The dose depends on many factors that are difficult to control: particle deposition in the lungs strongly depends on particle size, lung structure and breathing pattern, with the result that particle deposition and thus the deposited dose varies considerably among patients." (Brand, 1999, p. 724, second column, first paragraph). "Although all patients were carefully trained at the beginning of their inhalation therapy to perform inhalations deeply and slowly, the breathing pattern was quite different among patients (Fig. 2)." (Brand, 1999, p. 726, second column, last paragraph). As discussed above, Goodman adjusts the amount of medication administered, but it does not control or adjust tidal volume or respiratory flow. Therefore, Goodman does not disclose providing an optimal dose of at least one active ingredient of an aerosol to a desired section of a lung of a patient.

Amended independent claims 25, 43, and 44 also claims, in part, the step of "controlling an air flow through the inhalation device using the inhalation device during the controlled inhalation" (emphasis added).

As discussed above, Goodman discloses an MDI (metered dose inhaler) which monitors breathing maneuvers. The MDI in Goodman automatically triggers only once an inhalation flow threshold is reached. After reaching the threshold, the flow and volume are not controlled. Therefore, the dose deposited within the lungs still has a high variability. Goodman only discloses measuring the breathing maneuvers and administering drug based on the measured breathing maneuvers. While Goodman discloses guiding patients by audible or visible signals, this lacks efficacy. The Applicant has shown published clinical data from Koehler et al. that

show that, even when patients are guided, they do not inhale with the optimum flow rate and inhalation volume, as shown in the published clinical data from Köhler et al (Journal of Aerosol Medicine, 2005, submitted in the IDS dated July 11, 2006, copy attached). Köhler specifically states that "All the CF patients have been regularly trained for several years in manually triggered inhalation by a physiotherapist (i.e. to press the interrupter immediately prior to the start of inhalation and to release the interrupter immediately after the end). They were instructed to inhale deeply and slowly." (Köhler, page 388, column 1, third full paragraph). Despite these instructions, "it was found that inhalation with the electronically controlled inspiration flow by means of AKITA permitted a deposition that was 46% (range 3-162%) higher and more peripheral than the conventional mode.... The improvement noted for deposition was obviously attributable to the controlled breathing maneuver alone." (Köhler, page 391, first full paragraph). Goodman does not disclose controlling the air flow through the inhalation device. Goodman only discloses adjusting the drug administration based on the measured air flow.

In contrast, in the present invention as claimed in claims 25, 43 and 44, during the breathing maneuver, the air flow is controlled by the inhalation device. This means that each individual patient has to inhale step by step the desired drug amount with his individual inhalation maneuver, which guarantees that the entire inhalation is successfully completed. Goodman does not disclose controlling an air flow through the inhalation device.

Goodman does not disclose each and every element of Applicant's claims 25, 43, and 44. Therefore, it is respectfully suggested that the rejection of independent claims 25, 43 and 44 as being anticipated by Goodman is overcome. Claims 22, 28-32, 35, 36-39 and 42, being dependent upon and further limiting claim 25, should also be allowable for that reason, as well as for the additional recitations they contain. Reconsideration and withdrawal of the rejection of claims 22, 25, 28-32, 35-39 and 42are respectfully requested.

Rejections under 35 U.S.C. §103

Claims 23, 24, 33, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman in view of Wallace (6,024,089).

Applicants respectfully disagree, and believe the claims, as amended, are patentable over Goodman for the reasons given above in respect to the section 102 rejection of claim 25, from which claims 23, 24, 33, and 34 depend. The arguments above as to the novelty of claim 25 are repeated here by reference.

As amended, independent claim 25 claims, in part, "adjusting a respiratory flow or a tidal volume of the inhalation device based on the inhalation parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation". Goodman does not teach or suggest adjusting flow rate or tidal volume using individual patient parameters or aerosol parameters.

Goodman teaches adjusting aerosol delivery based on inspiratory flow, pause, expiratory flow, and tidal volume. Goodman only measures the patient's breathing pattern during respiration. Goodman does not teach or suggest adjusting respiratory flow or tidal volume and does not disclose adjusting respiratory flow or tidal volume based on individual patient parameters for the patient or aerosol parameters.

By adjusting the respiratory flow or tidal volume of the inhalation device, the method of the present invention is able to optimize the dose of the active ingredient of an aerosol that is applied to a desired section of a lung of a patient, as claimed in claim 25. Goodman does not teach or suggest an optimal dose of at least one active ingredient of at least one aerosol being applied to a desired section of a lung of the patient during the controlled inhalation. As the attached Brand paper explains (filed as part of an IDS dated July 11, 2006), it is very difficult to optimize dosage of an active ingredient for an aerosol from patient to patient without controlling the breathing pattern of the patient. Goodman adjusts the amount of medication administered, but it does not control or adjust tidal volume or respiratory flow. Therefore, Goodman does not teach or suggest providing an optimal dose of at least one active ingredient of an aerosol to a desired section of a lung of a patient.

Wallace does not provide what Goodman lacks. Wallace teaches a ventilation control system with a user-friendly interface. Wallace teaches to "start up the ventilator using a predetermined set of ventilator control settings deemed to be safe for the widest possible variety of patients" (column 3, lines 26-29, emphasis added). Wallace teaches using ventilator settings

safest for a wide variety of patients rather than any patient-specific settings. Wallace does not adjust any values in a patient specific manner. Wallace does not teach or suggest adjusting a respiratory flow or a tidal volume of an inhalation device based on inhalation parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during a controlled inhalation. In addition, Wallace can not teach or suggest an optimal dose of at least one active ingredient of at least one aerosol being applied to a desired section of a lung of a patient because Wallace does not even teach administering aerosols.

Combining Goodman and Wallace would not result in the present invention. Even if Wallace did adjust respiratory flow and tidal volume (which the Applicant does not concede), it does not do so in a way to optimize aerosol delivery because no aerosol administration is even taught or suggested in Wallace. Adding a Goodman metered dose inhaler to Wallace would not change this. The combination would instead result in an inhaler where the amount of medication delivered could be varied for a patient attached to a ventilator. Any adjustments in the tidal volume or respiratory flow in Wallace <u>would not be done for aerosol delivery, let alone to optimize that delivery</u>.

Any system capable of ventilating a patient by adjusting breathing parameters such as tidal volume or respiratory flow, which was also capable of administering aerosol in an optimized manner by adjusting the tidal volume or respiratory flow, would require a very complicated, interconnected control system between the ventilator and the inhaler. Neither reference teaches or suggests such a system. Even if the aerosol in Goodman's inhaler could somehow be delivered through the ventilator, any adjustments to breathing patterns in a ventilator are done to help the patient breathe through the ventilator, not to optimize any type of aerosol delivery. As a result, the combination that the Examiner is suggesting could actually be dangerous to the patient. The ventilator adjustments in a system that could also deliver aerosols could (and most likely would) deliver very incorrect doses to the patient.

Furthermore, there is no motivation to combine Goodman's inhaler with Wallace's ventilator, nor would the combination teach or suggest the present invention. Inhalers and

ventilators are very different devices with different functions. A person of ordinary skill in the art of inhalers would not combine elements from ventilator art with elements of an inhaler.

Goodman and Wallace, alone or in combination, do not teach or suggest all of the elements of claim 25. Therefore, it is respectfully submitted that claim 25 is not obvious over Goodman in view of Wallace. Claims 23-24 and 33-34, being dependent upon and further limiting claim 25, should also be allowable for that reason, as well as for the additional recitations they contain. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 22, 24, 25, 28-32, 34-39 and 42-44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gilmore *et al.* (5,931,160) in view of Rapoport *et al.* (5,490,502).

As amended, independent claim 25 claims, in part, the step of "individually adjusting the inhalation device to the patient to be treated by adapting a dosage of at least one aerosol on the basis of the inhalation parameters". Similarly, independent claims 43 and 44 claim, in part, the step of "individually adjusting the inhalation device to the patient to be treated by adapting a dosage of at least one aerosol on the basis of the individual patient parameters" and "individually adjusting the inhalation device to the patient to be treated by adapting a dosage of at least one aerosol on the basis of the aerosol parameters", respectively.

Gilmore teaches a ventilator control system, where a clinician can set breath parameters for a particular patient. Gilmore does not teach or suggest an inhalation device that is individually adjusted to a patient to be treated by adapting a dosage of at least one aerosol on the basis of the inhalation parameters. In fact, Gilmore does not teach or suggest an aerosol at all, and therefore, necessarily can not teach adapting a dosage of the aerosol.

Amended independent claim 25 also includes, in part, the substep of: "adjusting a respiratory flow or a tidal volume of the inhalation device based on the inhalation parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation". Claims 43 and 44 similarly claim "adjusting a respiratory flow or a tidal volume of the inhalation device based on the individual patient parameters such that an optimal dose of at least one active ingredient of at

least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation" and "adjusting a respiratory flow or a tidal volume of the inhalation device based on the aerosol parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation", respectively.

As discussed above, Gilmore does not teach or suggest aerosol dosing. Therefore, Gilmore also does not teach or suggest adjusting a respiratory flow or a tidal volume of an inhalation device so that an optimal dose of an active ingredient of an aerosol is applied to a section of a lung of a patient.

Rapoport does not provide what Gilmore lacks. Rapoport relates to a completely different field from the present invention. Rapoport teaches adjusting the positive airway pressure of a patient to an optimum value in the treatment of obstructive sleep apnea. The treatment of sleep apnea, i.e. the intermittent obstruction of the upper airway occurring during sleep, is in no way linked to the administering of a controlled inhalation of therapeutic aerosol for a patient during breathing maneuvers according to claims 25, 43 and 44.

More specifically, Rapaport does not teach or suggest individually adjusting an inhalation device to a patient to be treated by adapting a dosage of at least one aerosol on the basis of the inhalation parameters. In addition, Rapaport does not teach or suggest adjusting a respiratory flow or a tidal volume of the inhalation device based on the inhalation parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation. Rapaport does not teach or suggest any type of aerosol dosing.

Furthermore, there is no motivation to combine Gilmore's ventilator with Rapoport's sleep apnea breathing device, nor would the combination teach or suggest the present invention. Neither Gilmore nor Rapoport teach a method using an inhalation device. Each of the references teaches very different devices that perform different functions. A person of ordinary skill in the art of inhalers would not combine elements from ventilator or sleep apnea device art with elements of an inhaler.

Gilmore and Rapoport, alone or in combination, do not teach or suggest all of the elements of claims 25, 43 and 44. Therefore, it is respectfully suggested that the rejection of independent claims 25, 43 and 44 as being obvious over Gilmore in view of Rapoport is overcome. Claims 22, 24, 28-32, 34-39, being dependent upon and further limiting claim 25, should also be allowable for that reason, as well as for the additional recitations they contain. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 23 and 33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gilmore *et al.* (5,931,160) in view of Rapoport *et al.* (5,490,502) and further in view of Goodman (5,813,397).

Applicants respectfully disagree, and believe the claims, as amended, are patentable over Gilmore in view of Rapoport for the reasons given above in respect to the section 103 rejection of claim 25, from which claims 23 and 33 depend. The arguments above as to the anticipation and non-obviousness of claim 25 are repeated here by reference.

Goodman does not provide what Gilmore and Rapaport lack. Amended independent claim 25 includes, in part, the substep of "adjusting a respiratory flow or a tidal volume of the inhalation device based on the inhalation parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation". As discussed above with respect to the 102 rejection, Goodman does not teach or suggest adjusting respiratory flow or tidal volume. The MDI in Goodman is a manually-triggered conventional inhalation device. Goodman only teaches <u>measuring</u> the breathing maneuvers and administering drug based on the <u>measured</u> breathing maneuvers.

Combining Gilmore, Rapaport and Goodman would not result in the present invention. While Gilmore does set breathing parameters, it does not do so in a way to optimize aerosol delivery because no aerosol administration is even taught or suggested in Gilmore. Adding a Goodman metered dose inhaler to Gilmore would not change this. The combination would instead result in an inhaler where the amount of medication delivered could be varied for a patient attached to a ventilator. Any adjustments in the tidal volume or respiratory flow in Gilmore <u>would not be done for aerosol delivery, let alone to optimize that delivery</u>.

Any system capable of ventilating a patient by adjusting breathing parameters such as tidal volume or respiratory flow, which was also capable of administering aerosol in an optimized manner by adjusting the tidal volume or respiratory flow, would require a very complicated, interconnected control system between the ventilator and the inhaler. None of the three references teaches or suggests such a system. Even if the aerosol in Goodman's inhaler could somehow be delivered through the ventilator in Gilmore, any adjustments to breathing patterns in a ventilator are done to help the patient breathe through the ventilator, not to optimize any type of aerosol delivery. As a result, the combination the Examiner is suggesting could actually be dangerous to the patient. The ventilator adjustments in a system that could also deliver aerosols could (and most likely would) deliver very incorrect doses to the patient.

Furthermore, there is no motivation to combine Gilmore's ventilator with Rapoport's sleep apnea breathing device and Goodman's inhaler, nor would the combination teach or suggest the present invention. A sleep apnea breathing and a ventilator are both very different devices than an inhaler, and each device performs a different function. A person of ordinary skill in the art of inhalers would not combine elements from ventilator or sleep apnea device art with elements of an inhaler.

Gilmore, Rapoport, and Goodman, alone or in combination, do not teach or suggest all of the elements of claim 25. Therefore, it is respectfully submitted that claim 25 is not obvious over Gilmore in view of Rapoport and further in view of Goodman. Claims 23 and 33, being dependent upon and further limiting claim 25, should also be allowable for that reason, as well as for the additional recitations they contain. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 25, 43, and 44 were verbally rejected by the Examiner over Goodman in view of Gilmore during the in-person interview on November 30, 2007. Although this rejection was not part of the office action dated July 10, 2007, the Applicant is submitting arguments regarding this rejection to further prosecution of the application. The arguments regarding the anticipation of claims 25, 43, and 44 over Goodman are repeated herein by reference.

As amended, independent claim 25 claims, in part, "adjusting a respiratory flow or a tidal volume of the inhalation device based on the inhalation parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation". Claims 43 and 44 similarly claim "adjusting a respiratory flow or a tidal volume of the inhalation device based on the individual patient parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation" and "adjusting a respiratory flow or a tidal volume of the inhalation device based on the aerosol parameters such that an optimal dose of at least one active ingredient of at least one aerosol is applied to a desired section of a lung of the patient during the controlled inhalation", respectively.

Goodman does not teach or suggest <u>adjusting</u> flow rate or tidal volume using individual patient parameters or aerosol parameters. Goodman teaches <u>adjusting aerosol delivery</u> based on inspiratory flow, pause, expiratory flow, and tidal volume. Goodman only measures the patient's breathing pattern during respiration. Goodman does not teach or suggest <u>adjusting</u> respiratory flow or tidal volume and does not disclose adjusting respiratory flow or tidal volume based on individual patient parameters for the patient or aerosol parameters.

By adjusting the respiratory flow or tidal volume of the inhalation device, the method of the present invention is able to optimize the dose of the active ingredient of an aerosol that is applied to a desired section of a lung of a patient, as claimed in claim 25. Goodman does not teach or suggest an optimal dose of at least one active ingredient of at least one aerosol being applied to a desired section of a lung of the patient during the controlled inhalation. As the attached Brand paper explains (filed as part of an IDS dated July 11, 2006), it is very difficult to optimize dosage of an active ingredient for an aerosol from patient to patient <u>without controlling the breathing pattern of the patient</u>. Goodman adjusts the amount of medication administered, but it does not control or adjust tidal volume or respiratory flow. Therefore, Goodman does not teach or suggest providing an optimal dose of at least one active ingredient of an aerosol to a desired section of a lung of a patient.

Gilmore does not provide what Goodman lacks. Gilmore teaches a ventilator control system. Gilmore does not teach or suggest delivering aerosols, or optimizing a dose of an active ingredient of an aerosol to a section of a lung of a patient by adjusting the respiratory flow or tidal volume.

Combining Goodman and Gilmore would not result in the present invention. Gilmore does not adjust breathing parameters, such as respiratory flow or tidal volume, in a way to optimize aerosol delivery because no aerosol administration is even taught or suggested in Gilmore. Adding a Goodman metered dose inhaler to Gilmore would not change this. The combination would instead result in an inhaler where the amount of medication delivered could be varied for a patient attached to a ventilator. Any adjustments in the tidal volume or respiratory flow in Gilmore <u>would not be done for aerosol delivery, let alone to optimize that delivery</u>.

Any system capable of ventilating a patient by adjusting breathing parameters such as tidal volume or respiratory flow, which was also capable of administering aerosol in an optimized manner by adjusting the tidal volume or respiratory flow, would require a very complicated, interconnected control system between the ventilator and the inhaler. Neither reference teaches or suggests such a system. Even if the aerosol in Goodman's inhaler could somehow be delivered through the ventilator, any adjustments to breathing patterns in a ventilator are done to help the patient breathe through the ventilator, not to optimize any type of aerosol delivery. As a result, the combination the Examiner is suggesting could actually be dangerous to the patient. The ventilator adjustments in a system that could also deliver aerosols could (and most likely would) deliver very incorrect doses to the patient.

Furthermore, there is no motivation to combine Goodman's inhaler with Gilmore's ventilator, nor would the combination teach or suggest the present invention. Inhalers and ventilators are very different devices with different functions. A person of ordinary skill in the art of inhalers would not combine elements from ventilator art with elements of an inhaler.

Therefore, claims 25, 43, and 44 are not obvious over Goodman and Gilmore, alone or in combination.

Objections to the Specification

The specification was objected to as failing to provide proper antecedent basis for the claimed subject matter. More specifically, the Examiner stated that the original specification does not provide antecedent basis for the adjusting of a breathing parameter based on the inhalation parameters. Claims 25, 43 and 44 have been amended to overcome this objection. These amendments are fully supported by the Abstract of the application, as filed. Reconsideration and withdrawal of the objection are respectfully requested.

Rejection under 35 U.S.C. §112

Claims 25, 28-30 and 35-44 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. More specifically, the Examiner stated that the original specification does not provide support for the adjusting of a breathing parameter based on the inhalation parameters. Claims 25, 43 and 44 have been amended to overcome this rejection. These amendments are fully supported by the Abstract of the application, as filed. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicant believes the claims, as amended, are patentable over the prior art, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicants' attorney would advance the prosecution of the case to finality, he is invited to telephone the undersigned at the number given below.

"Recognizing that Internet communications are not secured, I hereby authorize the PTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file."

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Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations

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ABSTRACT: Treatment of systemic diseases by means of the inhalation route is hampered by uncertainties of the drug dose applied by inhalation. In this study, the hypothesis was tested that by standardization of the breathing maneuver used for inhalation, the interindividual variability of the dose deposited intrathoracically can be reduced. Therefore, breathing pattern during routine inhalations with jet nebulizers was measured in 18 patients with lung disease. Using monodisperse 3 μm particles, total deposition was then assessed for the measured spontaneous and for three controlled, slow breathing patterns. Particle deposition for the three controlled breathing patterns was additionally measured in 14 healthy subjects. The study has shown that within the study population the inhaled air volume and flow rate were quite different. Consequently, total particle deposition varied between 20 and 95%, depending on breathing pattern. For controlled, slow breathing patterns, deposition was on average higher, intersubject variability of deposition was smaller, and differences in deposition between healthy subjects and patients were negligible. Therefore, to perform efficient systemic treatment with aerosolized drugs, controlled, slow breathing patterns should be used. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 89: 724–731, 2000

Keywords: particle deposition; variability; breathing pattern

INTRODUCTION

For many decades it has been well known that drugs for systemic therapy may be administered by means of the lungs. Since 1925, it has been known that inhaled insulin decreases the blood glucose level.[1] Nowadays, despite considerable progress in nebulizer technique and increased knowledge about particle deposition in the lung and drug absorption from lung surfaces, insulin administration by means of the lung is still not established but has reached a state of advanced clinical studies. The main reason for this slowness of progress is related to uncertainties in the dose of drug administered by the inhalation route. The dose depends on many factors that are difficult to control: particle deposition in the lungs strongly depends on particle size, lung structure, and breathing pattern, with the result that particle deposition and thus the deposited dose varies considerably among patients.

In this study the hypothesis was tested that standardizing the breathing pattern decreases the intersubject variability of the dose deposited intrathoracically during inhalations of therapeutic particles generated with jet nebulizers. Therefore, in 18 patients deposition of inhaled monodisperse inert test particles was measured for the breathing pattern they used during routine inhalations with jet nebulizers and for three standardized patterns. In addition, particle deposition was

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measured in 14 healthy subject for these standardized patterns.

METHODS

Subjects

Eighteen patients, 12 men and 6 women, who were used to aerosol therapy with jet nebulizers and 14 healthy subjects, 8 men and 6 women, participated in this study (Table 1). Eight patients had chronic obstructive pulmonary disease, seven patients had bronchial asthma, one patient had bronchiectasis, one patient had silicosis, and one patient had primary ciliary dyskinesis. Conventional pulmonary function tests were performed by use of a Jäger-Masterlab (Erich Jaeger GmbH, Würzburg, Germany). Relative values of the lung function parameters (%pred) were calculated as proposed by the European Community for Coal and Steel.[2] Informed written consent was obtained from each subject. The study protocol was approved by the Ethics Committee of the Medical School of the Ludwig-Maximilians-University (Munich, Germany).

Spontaneous Breathing Patterns

The breathing pattern of patients during routine inhalations with jet nebulizers (Pari-LC+ nebulizers, Pari GmbH, Starnberg, Germany, pressure 0.17 M Pa) was measured as follows: An ultrasonic transient-time flowmeter (TUBA, GHG AG, Zürich, Switzerland) was connected to the Venturi channel (air inlet) of the nebulizer. The analogous flow signal was recorded by a personal computer (Intel 386 CPU) with a analog-digital converter (Data Translation DT2821), and the flow rate through the nebulizer nozzle was added. This air flow through the nebulizer nozzle was measured for each nebulizer before inhalation. All patients were instructed to perform inhalations as usual until 2.5 mL of a salbutamol inhalation solution (GlaxoWellcome, 1.5 mg salbutamolsulphate in isotonic NaCl solution) was completely nebulized. From the recorded flow rates of each breath the average spontaneous tidal volume, V_t, and flow rate, Q_t, were calculated for each patient.

Deposition

To measure total deposition of aerosol for various breathing patterns, a monodisperse inert test aerosol consisting of di-2-ethylhexyl sebacate (DEHS) droplets was used. Deposition measurements were performed using a device in which a laser aerosol photometer[3] is combined with an piston-type ventilator, allowing the subject to inhale particles at controlled breathing patterns (Fig. 1). The ventilator has a volume of 2 L and is driven by a computer-controlled step motor. A system of computer-controlled magnetic valves allows us to connect the ventilator to ambient air, to an aerosol supply, or to a mouthpiece at which the subject wearing a noseclip is located. After the ventilator was filled with aerosol, the subject tried to inhale at the mouthpiece, causing an underpressure that initiated the step motor. Thus, aerosol is inhaled at a preselected flow rate, Q_i. After inhalation of the desired aerosol volume, the direction of the ventilator was inverted and the subject exhaled into the ventilator at the preselected flow rate.

During the entire breathing cycle the laser aerosol photometer recorded the respired particle number concentration. Aerosol particle deposition, D, was calculated by integrating the particle number concentration, C, over the inhaled, V_i,

Table 1. Lung Function Parameters of the Study Population

Parameter	Patients		Normals	
Number	18		14	
Sex	12 m/6 f		8 m/6 f	
Age (yrs)	60 ± 16		35 ± 6	
VC	3.1 ± 0.91	90 ± 19%pred	5.3 ± 11	113 ± 10%pred
TLC	6.4 ± 1.11	103 ± 14%pred	6.9 ± 11	107 ± 7%pred
ITGV	4.4 ± 1.51	143 ± 42%pred	3.6 ± 0.71	112 ± 19%pred
FEV_1	1.78 ± 1.11	66 ± 34%pred	4.0 ± 0.91	106 ± 13%pred

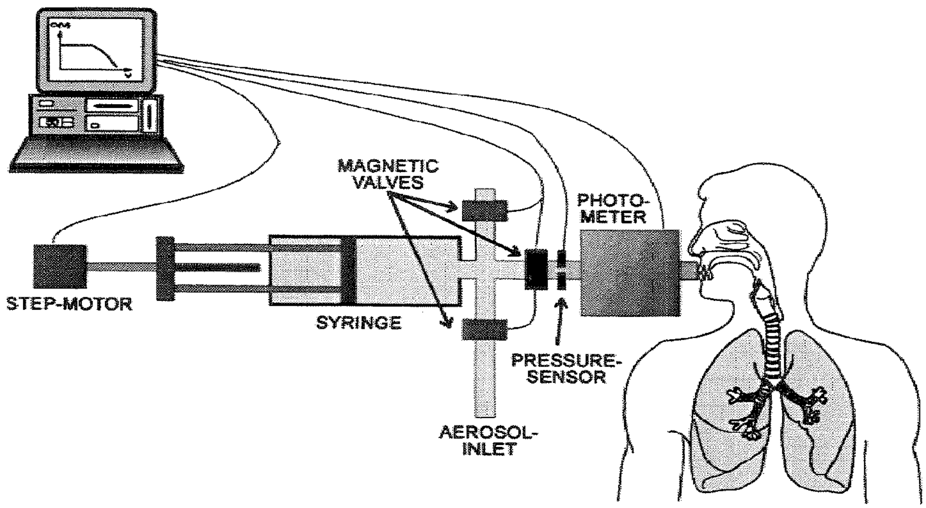

Figure 1. Schematics of the device for the measurement of lung deposition.

and exhaled volume, V_e:

$$D = 1 - \frac{\int_{V_e} C dV}{\int_{V_i} C dV}$$

In this study the following breathing patterns were performed by each subject:

Spontaneous breathing:
$V_i = V_e = V_t, \quad Q_i = Q_e = Q_t$

Very slow controlled breathing:
$V_i = V_e = 1L, \quad Q_i = Q_e = 100\ cm^3/s$

Slow controlled breathing:
$V_i = V_e = 1\ L, \quad Q_i = Q_e = 250\ cm^3/s$

Normal controlled breathing:
$V_i = V_e = 1L, \quad Q_i = Q_e = 500\ cm^3/s$

For each breathing pattern particle deposition was measured twice in each subject. Healthy subjects performed only the three standardized breathing patterns.

Particle Generation and Classification

Monodisperse di-2-ethylhexyl sebacate (DEHS) droplets were produced by heterogeneous nucleation of DEHS vapor on NaCl nuclei in a nitrogen atmosphere using a Topas SLG 270 generator (Palas, Karlsruhe, FRG). The aerosol was then diluted with particle-free air to achieve a particle number concentration of $2 \cdot 10^4\ cm^{-3}$. Particle size was measured in a convection-free sedimentation cell and throughout the study was 2.98 μm ± 0.05 μm, a typical particle diameter for medical nebulizers.[4]

Data Evaluation

All statistical calculations were performed using Statgraphics Plus for Windows 2.0 on a personal computer (Pentium II CPU). The significance of differences between group averages was tested using the Student's *t* test. Correlation analysis was performed using Pearson product-moment correlation analysis. The requested level for significance was $P = 0.05$.

RESULTS

Although all patients were carefully trained at the beginning of their inhalation therapy to perform inhalations deeply and slowly, the breathing pattern was quite different among patients (Fig. 2). Some patients inhaled with a tidal volume of about 250 cm^3 and flow rates less than 200 cm^3/s, others inhaled about 2,000 cm^3 with flow rates close to 1,000 cm^3/s. The intraindividual variability of the tidal volume was 25 ± 10% and that of flow rate 22 ± 10%. There was a strong correlation

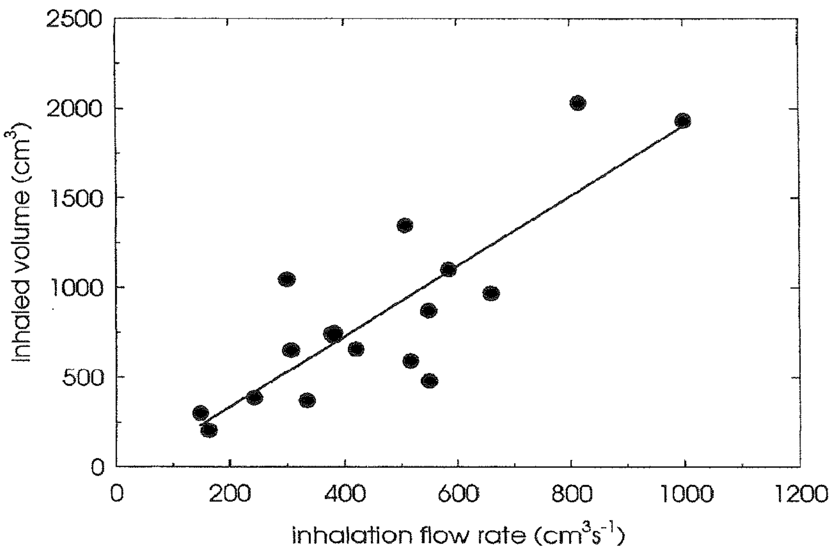

Figure 2. Tidal volume and flow rate measured in 18 patients with lung disease during spontaneous inhalations with a jet nebulizer.

between tidal volume and inhalation flow rate ($r = 0.84$, $P < 0.0001$): Thus, patients inhaling a large volume inhaled with a high flow rate; patients inhaling small volumes inhaled slowly with the result that the time of inhalation was nearly the same in all patients (1.8 ± 0.62 s).

Deposition of 3-μm particles for spontaneous breathing pattern correlated strongly with the flow rate ($r = 0.76$, $P = 0.0002$) (Fig. 3) and the tidal volume ($r = 0.75$, $P = 0.0003$): patients inhaling a large volume at a high flow rate showed high aerosol deposition and vice versa. Average

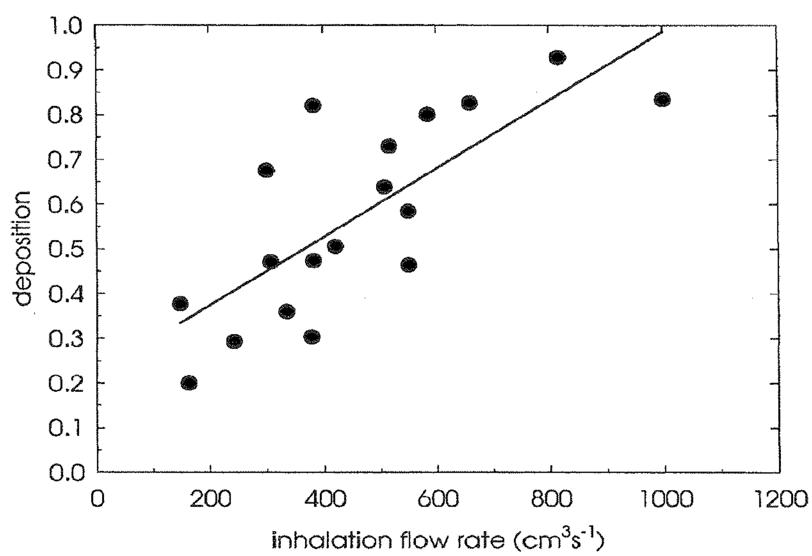

Figure 3. Particle deposition measured with test particles in 18 patients with lung disease as a function of inhalation flow rate.

total deposition in all patients was (57 ± 22%), exhibiting large intersubject variability: one patient showed deposition as low as 20%, whereas another patient reached deposition values of 95%. This variability was considerably reduced for controlled breathing (Fig. 4). Deposition was highest and the variability was lowest for very slow controlled breathing (79 ± 7%). For the slow breathing pattern deposition was significantly lower than for the very slow pattern (70 ± 10 %, t test: $P = 0.01$). The normal breathing pattern showed similar deposition values as the slow pattern (71 ± 13%, t test, not significant). There was a significant correlation between deposition and flow rate ($r = -0.20, P = 0.04$). For all controlled breathing patterns there were no significant differences in aerosol deposition between patients and healthy subjects (Fig. 5). However, deposition in patients tended to be greater for the largest flow rate, and the variability of deposition was larger in patients for all flow rates. In healthy subjects deposition decreased significantly with increasing flow rate ($r = 0.74, P < 0.0001$). Again, deposition for the very slow breathing pattern was highest (79 ± 7%), lower for the slow breathing pattern (71 ± 4%, $P < 0.0001$), and again lower for the normal breathing pattern (65 ± 7%, $P = 0.007$). At a flow rate of 500 cm^3/s, deposition in patients correlated negatively with the extent of airway obstruction as measured by FEV_1 ($r = 0.72, P = 0.002$) (Fig. 6). Except for this obstruction dependency of deposition, no dependency on the kind of lung disease was observed in patients. At lower flow rates and in healthy subjects no significant correlations were observed (Fig. 7).

DISCUSSION

In this study total particle deposition was measured, but it was not possible to distinguish between extrathoracic, bronchial, and alveolar deposition. However, the total deposition values measured in this study are similar to the values given by a common deposition model.[5] For the very slow breathing pattern and for 3-μm particles this model delivers a total deposition of 80%, which is in excellent agreement with the data measured in this study, and an extrathoracic deposition of 1.6%. For the faster patterns total deposition is 69 and 58%, and the extrathoracic deposition increases to 4 and 7.5%. Bronchial deposition given by this model is 9% for the very slow pattern and 3.5 and 3.6% for the faster inhalations. Because extrathoracic deposition is supposed to be similar to that observed in healthy subjects in patients with lung disease, we conclude that total deposition measured in this study is a reasonable measure for intrathoracic deposition in humans.

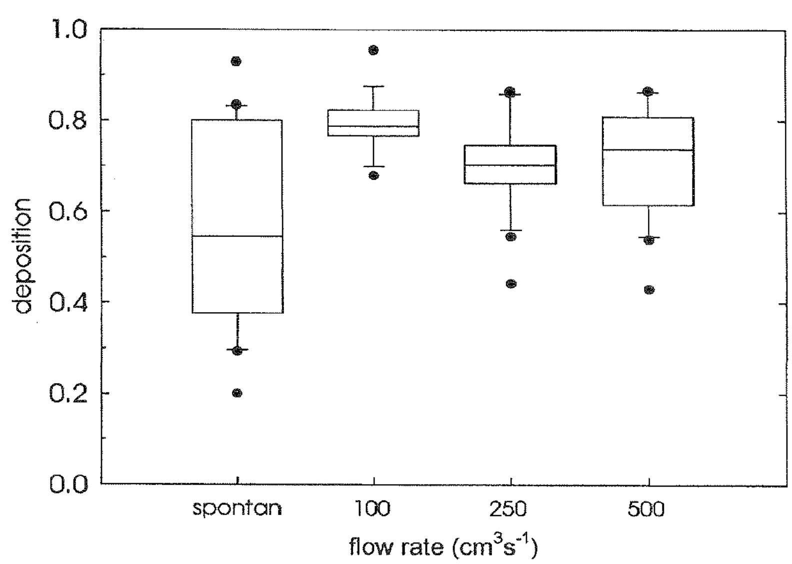

Figure 4. Particle deposition in 18 patients with lung disease at various breathing patterns.

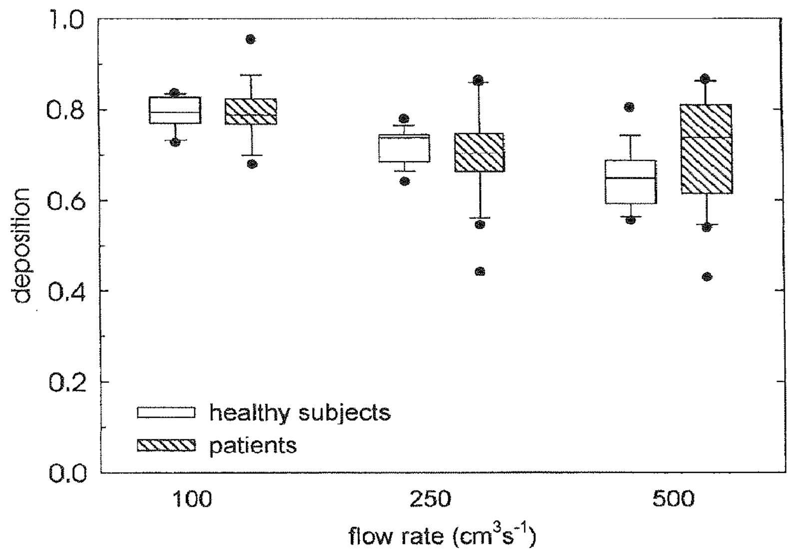

Figure 5. Particle deposition measured in 18 patients with lung disease and in 14 healthy subjects at three different breathing patterns.

For inhalation drug delivery requiring a precise dosage, the large intersubject variability of total deposition measured in this study for a spontaneous inhalation pattern is unacceptable. The data of this study show that the variability of particle deposition within the respiratory system can be considerably reduced if the breathing pattern is controlled. The variability of deposition for the very slow breathing pattern was about three times smaller than the variability for the spontaneous pattern. This reduction in intersubject variability was air-flow rate dependent (Fig. 5). For slow and very slow flow rates deposition in healthy subjects and in patients is nearly identi-

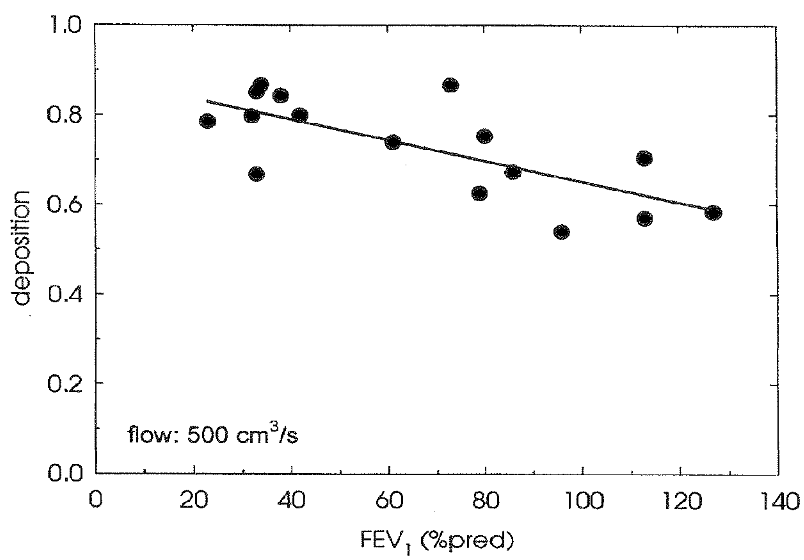

Figure 6. Particle deposition in 18 patients with lung disease at a inhalation flow rate of 500 cm^3/s as a function of the forced expiratory volume in 1 s (FEV_1).

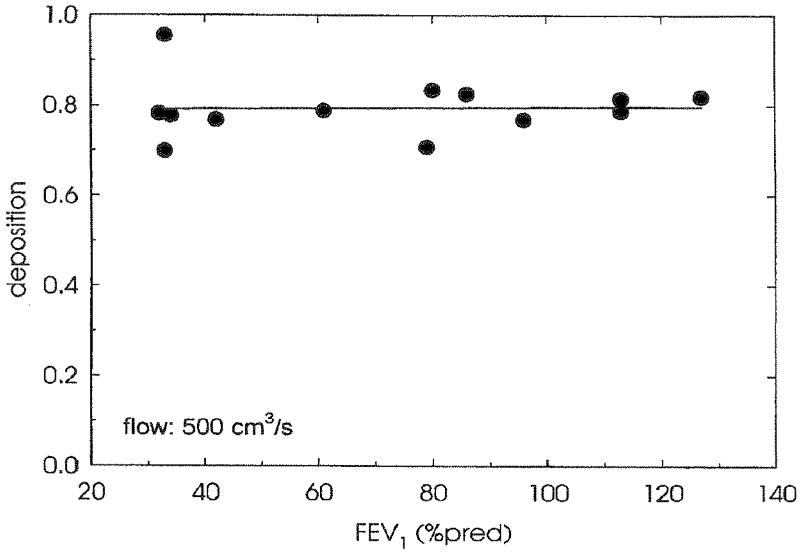

Figure 7. Particle deposition in 18 patients with lung disease at a inhalation flow rate of 100 cm^3/s as a function of the forced expiratory volume in 1 s (FEV_1).

cal. Only for the highest air flow rate of 500 cm^3/s, patients tended to have higher deposition values than healthy subjects. If we assume that extrathoracic deposition is small, this difference may be explained by particle impaction in obstructed airways at higher flow rates[6–10] The strong correlation between FEV_1 and particle deposition (Fig. 6) illustrates that patients with normal FEV_1 (i.e., without airway obstruction) have the same deposition values as healthy subjects, whereas patients with decreased FEV_1 (i.e., with airway obstruction) show increased total deposition. This increase of total deposition in patients with airway obstruction is presumably due to increased inertial deposition within conducting airways. Because total deposition in patients and healthy subjects is the same for the very slow breathing pattern, it may be concluded that by inhaling very slowly, inertial deposition at obstructed airways can be prevented.

The implications of these results for an improvement of inhalation therapy are obvious. If a drug shall be applied to the lung periphery with high efficacy and low variability, inhalation should be performed slowly and controlled. In this case deposition is high (about 80%), the intersubject variability is low (9% for patients and 5% for subjects without lung disease), and deposition in obstructed airways may become negligible.

CONCLUSION

This study has shown that the intersubject variability of total particle deposition can be considerably reduced if the breathing pattern is controlled. If the inhalation flow rate is low, the variability is low and deposition at bronchial obstructions is supposed to be negligible. Therefore, the controlled breathing pattern with low flow rate is most suitable for targeting the lung periphery and thus for systemic aerosol therapy. If hormones like growth hormones or estradiol, heparin for surgery patients,[11,12] α_1-antitrypsin for patients with α_1-antitrypsin deficiency,[13] or prostacyclin for patients with pulmonary hypertension[14] are administered by the inhalation route, this standardization of breathing patterns appears to be necessary.

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Lung Deposition after Electronically Breath-Controlled Inhalation and Manually Triggered Conventional Inhalation in Cystic Fibrosis Patients

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ABSTRACT

The present work aimed to investigate whether lung deposition can be improved by using a device that optimizes the breathing pattern through electronic control. The relative lung deposition was estimated by inhalation of the marker substance, sodium cromoglycate (SCG), and measurement of urinary excretion of SCG. Thirteen cystic fibrosis (CF) patients (aged 8–20 years) received 20 mg of SCG as nebulizer solution by means of (a) conventional inhalation (Parimaster + Pari LC Star nebulizer, manual interrupter) and (b) electronically breath-controlled inhalation (AKITA + Pari LC Star nebulizer). Inhalations were trained and supervised by a physiotherapist. Patients were asked to provide answers to a questionnaire about the convenience of electronically breath-controlled inhalation. Urine was collected in five fractions until 12 h p.a., and the excreted SCG was determined by means of high-performance liquid chromatography (HPLC). Following breath-controlled inhalation, the amount of SCG excreted in urine was significantly greater than after conventional inhalation (2.22 ± 0.61 mg vs. 1.63 ± 0.59 mg, $p < 0.001$). The absorption half-life for SCG following breath-controlled inhalation was significantly shorter when compared with conventional inhalation (78 ± 23 min vs. 107 ± 29 min; $p < 0.01$), suggestive of a more peripheral deposition for the former. Ninety-two percent of the patients judged that the electronically breath-controlled inhalation was good or very good. In conclusion, inhalation with an electronically optimized breathing pattern yields a greater and more peripheral lung deposition of SCG compared with the manually triggered conventional nebulizer technique in CF patients with several years of aerosol inhalation experience.

Key words: inhalation, controlled breathing, lung deposition, sodium cromoglycate, urinary excretion, cystic fibrosis

INTRODUCTION

Direct delivery of pharmacological agents to the intrathoracic airways by aerosol administration is the preferred route for the treatment of pulmonary diseases. However, deposition of high amounts to peripheral lung regions is hindered by the low effectiveness of the conventional inhalation technique. Only a small proportion of the initial dose in the inhalation device reaches

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the lungs while the remainder is swallowed, exhaled into the atmosphere, or remains in the nebulizer. Following inhalation with breath-enhanced jet nebulizers, lung deposition is less than 20% of the nominal dose.[1–3]

Using the AKITA system connected to the jet nebulizer, the aerosol generation automatically occurs throughout the inspiration phase only. Furthermore, the inhalation flow rate and the inhalation volume, adapted to the patient's individual inspiratory capacity, are electronically controlled. Inhaling with this optimal breathing pattern, lung deposition was seen to be higher and more peripheral compared with employing conventional devices.[4–6]

Theoretically, while manually triggered conventional inhalation with a deliberately slow and deep inspiration should offer comparable conditions of inhalation, many patients and healthy volunteers fail to make efficient use of a manual interrupter and accomplish an adequate breathing manoeuvre during inhalation. However, cystic fibrosis (CF) patients have years of inhalation experience, and they are proficient at manual triggering and adequate breathing maneuvers. Therefore, the question arises whether or not such patients can achieve an improvement in lung deposition through electronic control of inhalation by the AKITA system, where the patient adopts a preset individually optimized breathing maneuver.

An established method adapted to evaluate the relative lung deposition (relative lung bioavailability) involves inhalation of sodium cromoglycate (SCG) as a marker substance and measurement of urinary drug excretion.[7–9] SCG is well absorbed from the lungs, but the fraction impacted on the oropharynx is swallowed and poorly absorbed (<1%) from the gastrointestinal tract.[7,10] The rate of drug absorption from the airways increases as SCG is deposited more peripherally.[11,12] Therefore, pharmacokinetic calculation of the SCG absorption half-life allows both the quantity and the depth of pulmonary deposition to be compared.[11–14]

It was the purpose of the present investigation to compare the pulmonary drug deposition in CF patients following conventional manually triggered inhalation and AKITA breath-controlled inhalation using the Pari LC Star jet nebulizer by measuring urinary excretion of the marker substance, SCG.

MATERIALS AND METHODS

Patients

Thirteen CF patients aged 8–20 years (eight male, five female) with *Pseudomonas aeruginosa* colonization participated in the study. The main characteristics and lung function data are presented in Table 1. During the study, the patients had no acute pulmonary exacerbations or upper airway diseases. Renal and hepatic functions were normal in all patients, represented by serum con-

TABLE 1. PATIENTS' DEMOGRAPHICS AND LUNG FUNCTION

Patient no.	*Age, (years)*	*Gender, m/f*	*Size, cm*	*Weight, kg*	*Shwachman's score*	*FEV_1, % pred.*	FVC, %pred.	$MMEF_{25-75}$ % pred.
1	19	m	188	77	75	72	81	46
2	14	m	179	59	75	106	98	107
3	10	f	146	38	70	98	91	86
4	18	m	176	61	75	79	82	58
5	13	m	148	38	75	89	87	79
6	13	m	157	50	75	80	91	49
7	14	f	136	28	40	38	49	14
8	12	m	147	31	75	80	80	58
9	20	m	182	67	75	75	92	43
10	8	f	132	22	75	109	95	131
11	18	f	166	51	75	95	99	71
12	11	f	147	32	75	100	91	90
13	18	m	180	58	75	79	102	45
Mean	14		160	47	72	85	88	67
SD	4		19	17	10	19	13	31

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; $MMEF_{25-75}$, maximum mid-expiratory flow between 25% and 75% of forced vital capacity; SD, standard deviation.

centrations of urea, creatinine, aspartate amino transferase, alanine amino trasferase, gamma-glutamyl transpeptidase, and choline esterase in a normal range.

Study design

The SCG test inhalation was designed as a randomized crossover trial. The patients, once admitted to the study, were alternatively assigned to group A or B. Group A first performed the manually triggered inhalation and then, after a 2-day washout period, the breath-controlled inhalation. Group B performed the procedure in the inverse sequence. The patients inhaled the aerosol through a mouthpiece while wearing a noseclip. The solution used for inhalation contained 20 mg of SCG (2 mL of 1% Intal® nebulizer solution; Aventis Pharma, Bad Soden, Germany).

The patients' current pulmonary function was measured on each day of the study, immediately prior to test inhalation, using a Pneumoscope® unit (Jäger, Würzburg, Germany). A physiotherapist supervised all the test inhalations and recorded their duration.

Manually triggered conventional inhalation. Parimaster® compressor and Pari LC Star® nebulizer were fitted with manual interrupter (Pari GmbH, Starnberg, Germany).

For intermittent aerosol delivery, the manual interrupter was operated to coincide with the inhalation phase of breathing. All the CF patients have been regularly trained for several years in manually triggered inhalation by a physiotherapist (i.e. to press the interrupter immediately prior to the start of inhalation and to release the interrupter immediately after the end). They were instructed to inhale deeply and slowly. Inhalation was completed as soon as the nebulized mist was no longer visible to the naked eye. Manual triggering was trained for the last time 1 day prior to the test inhalation.

Electronically breath-controlled inhalation. AKITA® device (INAMED GmbH, Gemünden, Germany) was used with the Pari LC Star® nebulizer (Pari, Starnberg, Germany).

Inhalation was controlled by the AKITA system such that the connected LC-Star nebulizer produced aerosol during the inhalation phase only. An optimized breathing maneuver was programmed for each patient through an individual smart card. The inhalation volume (IV) was individualized, taking into account the patient's inspiratory capacity (IC) by using the following equation: $IV = 1.2 * e^{1.3 / IC} + 0.23$ [L]. The flow rate was fixed to 200 mL/sec. The patient received feedback instructions from the display of the AKITA device. Inhalation was begun by the patient drawing on the mouthpiece, at which time the nebulizer was supplied with compressed air (to produce aerosol), and a defined volume of auxiliary air was delivered to the patient by positive pressure for a particular time interval via the AKITA device. At the end of the inhalation phase, purging was performed with 200 mL of auxiliary air, with no aerosol admitted. The patient did not use the mouthpiece for exhaling.

The CF patients were given a first-time introduction to the AKITA system 1 day prior to the test inhalation, and the physiotherapist trained the CF patients on how to inhale with this new inhalation device.

The mass median diameter (MMD) and the geometric standard deviation (GSD) of aerosols were determined using a Helos 1440, R3 optics particle measurement system (Sympathek GmbH, Claustal-Zellerfeld, Germany)

Measurement of SCG

Urine was collected immediately before inhalation as well as 2, 4, 6, 8, and 12 h post-dose. The urine volume was recorded, and 10-mL aliquots were frozen at −20°C until SCG analysis by high-performance liquid chromatography (HPLC) as described elsewhere.[13] The portion of SCG dose retained in the nebulizer after inhalation was rinsed out with water and analyzed following dilution, as appropriate.

Pharmacokinetics

Urinary excretion data was used for pharmacokinetic calculations.[15] Following inhalation, absorption of SCG becomes rate-limiting (absorption rate < elimination rate) and therefore "flip-flop" kinetics apply.[11,16] This means that the declining phase of the urinary excretion rate plot represents the absorption and not, as is more common, the elimination. The absorption rate constant (k_a) was determined by measuring the slope of the logarithm of the SCG excretion rate plotted against time (mid-point of collection interval), using linear regression analysis.[15] The

absorption half-life ($t_{1/2a}$) was calculated by $t_{1/2a} = 0.693/k_a$. The absorption rate can be taken as an indirect measure of the depth to which SCG penetrates into the lung. The more peripheral the deposition of SCG, the greater should be the absorption rate (i.e., the shorter the absorption half-life measured).[11,12] Since preliminary investigations have revealed that SCG is not detectable in urine after 12 h, the amount of SCG excreted at 12 h post-dose was considered the total amount excreted.

Questionnaire

Following the electronically breath-controlled inhalation, the patients were asked about the convenience of the AKITA device. The questionnaire presented to the patients and answered through a visual score had already been used in a previous study.[17] The patients were requested to quantify their subjective impression for three questions by indicating a cross on a scale, with scores ranging from 0 to 10 being possible in each case.

1. What is your general impression of the AKITA [very good to very poor]?
2. What is your assessment of the speed of inhalation using AKITA [too slow to too fast]?
3. What is your assessment of the time of inhalation for one breath using AKITA [too long to too short]?

The scale was gauged from the left to determine the scores.

Statistical analysis

Statistical evaluation was made by means of SPSS for MS Windows Release 10.0. Normal distribution of the variables was proved using the Kolmogorov-Smirnov test. Intra-individual comparison was made by means of the two-tailed paired *t*-test. The correlation between two variables was determined by using Pearson's coefficient of correlation. For all evaluations, the level of significance accepted was $p = 0.05$. Results are given as mean ± SD.

Informed consent statement

The study protocol was approved by the Human Ethics Committee of the Otto von Guericke University Medical Faculty, and written informed consent was obtained from all patients or their parents.

RESULTS

The lung functions of the 13 CF patients did not significantly differ prior to manually triggered conventional inhalation of SCG versus AKITA breath-controlled inhalation (Table 2). The droplet size produced by the Pari LC Star nebulizer was almost identical for the aerosols produced by the two sets of inhalation equipment. The MMD (GSD) was 3.57 μm (1.77 μm) for the conventional inhalation and 3.55 μm (1.79 μm) for the AKITA breath-controlled inhalation.

Using the AKITA breath-controlled mode, patients terminated inhalation after a time interval significantly shorter than that noted with conventional equipment (6.6 ± 0.9 min vs. 8.7 ± 2.4 min; $p = 0.007$). The difference between SCG amounts retained in the nebulizers, however, was not statistically significant (10.5 ± 1.0 mg vs. 10.3 ± 1.4 mg; $p = 0.582$).

The rates of urinary excretion of SCG during the 12-h collection period post dosing are shown in Figure 1. Following inhalation with manually triggered conventional equipment and with the

TABLE 2. LUNG FUNCTION MEASURED IMMEDIATELY PRIOR TO CONVENTIONALLY MANUALLY TRIGGERED INHALATION (LC STAR) AND BREATH CONTROLLED INHALATION (AKITA + LC STAR) (N = 13)

		LC Star		*AKITA = LC Star*		
		Mean	*SD*	*Mean*	*SD*	p[a]
FVC	(L)	3.18	1.35	3.27	1.41	0.295
FEV_1	(L)	2.54	0.95	2.55	0.97	0.824
$MMEF_{25-75}$	(L/s)	2.31	0.99	2.30	0.99	0.980

[a]Two-tailed paired *t*-test.

FVC, forced vital capacity; FEV_1 forced expiratory volume in 1 sec; $MMEF_{25-75}$, maximum mid-expiratory flow between 25% and 75% of forced vital capacity.

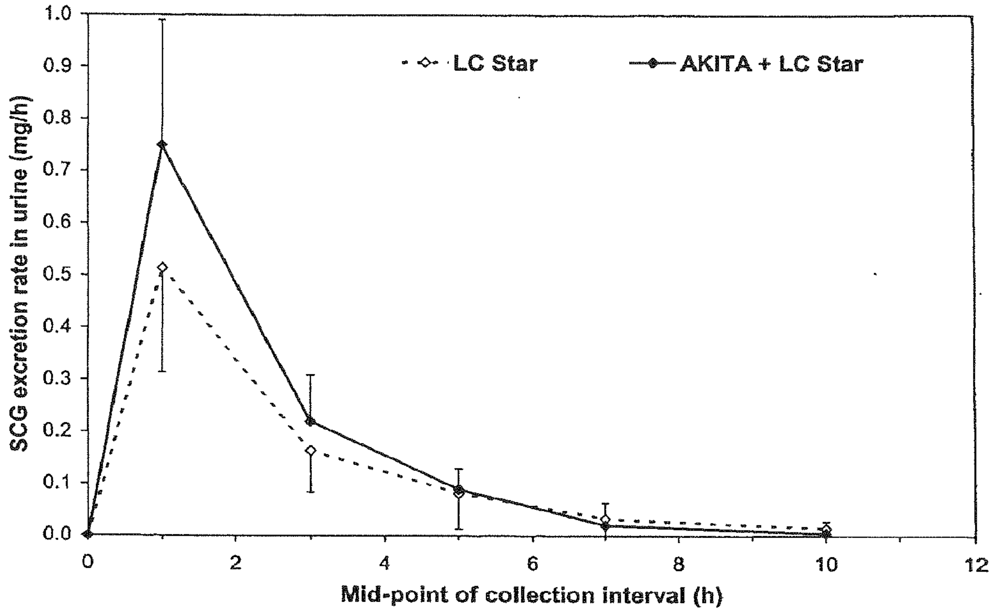

FIG. 1. Rate of urinary excretion of SCG (mean and SD) during the 12-h collection period following 20-mg dosing after conventional manually triggered inhalation (LC Star) and AKITA breath-controlled inhalation (LC Star + AKITA) in 13 CF patients.

AKITA breath-controlled mode, the rate of SCG urinary excretion decreased from 0.51 ± 0.20 and 0.75 ± 0.25 mg/h (0–2 h p.a.) to 0.03 ± 0.03 and 0.02 ± 0.03 mg/h (6–8 h p.a.), respectively. Hence, after 8 h, excretion of SCG was almost complete, being 96.1 ± 3.4% and 97.1 ± 2.9% of the total amount measured in urine during the 12-h collection period.

The total amounts of excreted SCG seen when using AKITA breath-controlled equipment were significantly higher when compared with use of the conventional mode (2.22 ± 0.61 mg vs.1.63 ± 0.59 mg; $p < 0.001$; Fig. 2). Thus, on average, pulmonary deposition was 46% (range 3–162%) greater compared with conventional inhalation. The SCG absorption half-lives determined for breath-controlled inhalation were significantly shorter than those noted for conventional inhalation (78 ± 23 min vs. 107 ± 29 min; $p = 0.006$; Fig. 3)—that is, absorption took place more peripherally compared with conventional inhalation. Also, the only patient (no. 7) with more severe lung disease exhibited an improvement of lung deposition after AKITA-controlled inhalation (SCG excretion of 1.55 vs. 1.01 mg and absorption half-life of 55 vs. 112 min) compared with manually triggered inhalation.

The possible influence of the patients' pulmonary function on pulmonary deposition (amount and absorption half life) was checked for all standard lung function parameters (absolute value and % predicted). No correlation between deposition and lung function variables was seen for the conventional inhalation. In contrast, for AKITA breath-controlled inhalation a statistically significant correlation was noted between FVC (L) and the amount of SCG excreted ($r = 0.579$; $p = 0.038$).

Figure 4 shows the answers to the questionnaire about the convenience of the breath-controlled inhalation using the AKITA device. An assessment of "good to very good" (median score 0.8; range 0.0–8.7) for the inhalation in general (Fig. 4A) was given by 92% of the patients (12 of 13). Eighty-five percent of the patients (11 of 13) considered the flow rate of 200 mL/sec (Fig. 4B) neither too high nor too low (median score 5.0; range 2.2–7.9). The time of inspiration (Fig. 4C) was considered neither too short nor too long by 69.2% of the patients (nine of 13; median score 4.9; range 1.2–9.8). Those two patients who provided the poorest assessment of the device reported dissimilar experience of the specified breathing parameters. They gave the minimum and the maximum score, as applicable, for the

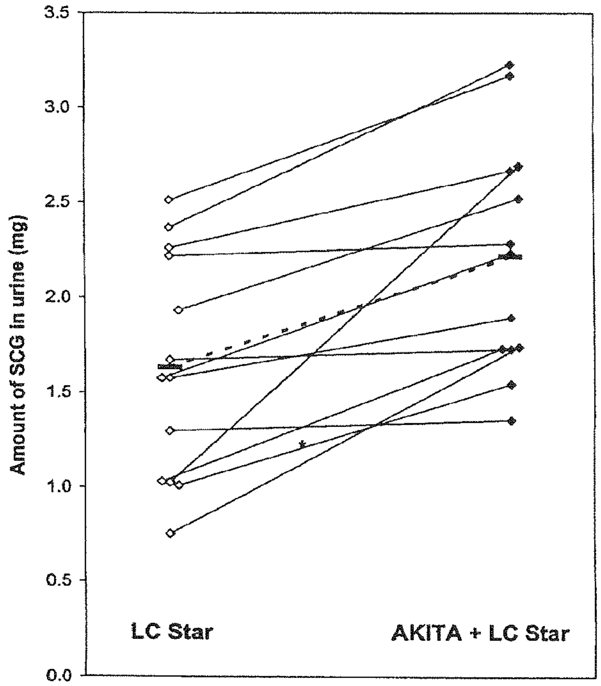

FIG. 2. Individual amounts of SCG recovered over the 12-h period following 20-mg dosing after conventional manually triggered inhalation (LC Star) and AKITA breath-controlled inhalation (LC Star + AKITA) in 13 CF patients. The dashed line connects the means (1.63 mg ± 0.59 mg vs. 2.22 mg ± 0.61 mg; $p < 0.001$). *Patient 7 with more severe lung function.

flow rate and the inspiration time (Fig. 4, patients 9 and 12).

DISCUSSION

This study was undertaken to compare the pulmonary deposition following inhalation with the LC Star breath-enhanced jet nebulizer working in both conventional manually triggered mode and AKITA breath-controlled mode. It was found that inhalation with the electronically controlled inspiration flow by means of AKITA permitted a deposition that was 46% (range 3–162%) higher and more peripheral than the conventional mode. Given the identical droplet size of the aerosols produced with both inhalation methods, the improvement noted for deposition was obviously attributable to the controlled breathing maneuver alone. Similarly, Brand et al.[6] studying adult patients with mild-to-severe chronic obstructive pulmonary disease after inhaling radiolabeled Prolastin® with the AKITA-controlled LC Star nebulizer, found both a greater total deposition and a higher peripheral deposition compared with the manually triggered LC-Star nebulizer and also compared with the HaloLite® device.

In the HaloLite® device, inhalation is electronically controlled by an adaptation of the nebulizing process to patients' arbitrary breathing pattern. An aerosol bolus is introduced into the inhalation at the beginning of each breath, followed by an aerosol-free interval. The AKITA device too is based on adapting the nebulizing process to the inspiration phase and adopting an aerosol-free interval at its end. Moreover, however, the breathing pattern is controlled (i.e., each patient inhales the largest possible volume that is still convenient for them, and the inhalation flow rate is fixed to values which are slow enough, 200 mL/sec, to prevent deposition by impaction in obstructed proximal airways).[4,6] Hence, com-

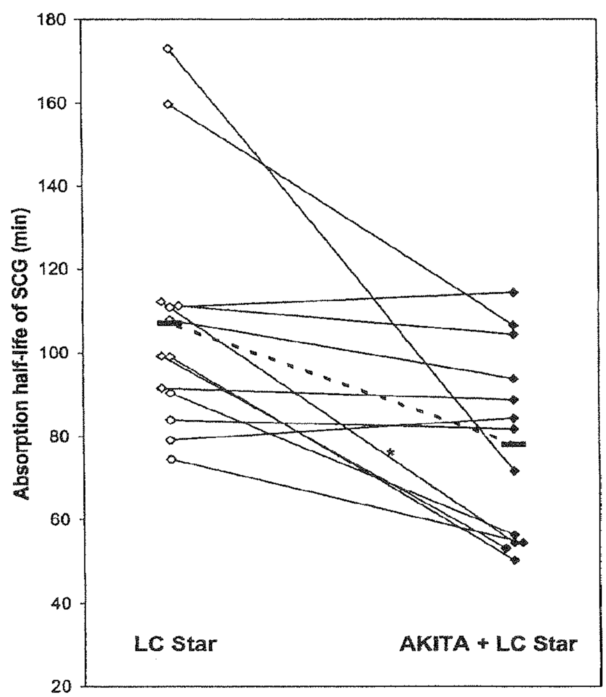

FIG. 3. Individual SCG absorption half-life following conventional manually triggered inhalation (LC Star) and AKITA breath-controlled inhalation (LC Star + AKITA) in 13 CF patients. The dashed line connects the means (107 min ± 29 min vs. 78 min ± 23 min; $p = 0.006$). *Patient 7 with more severe lung function.

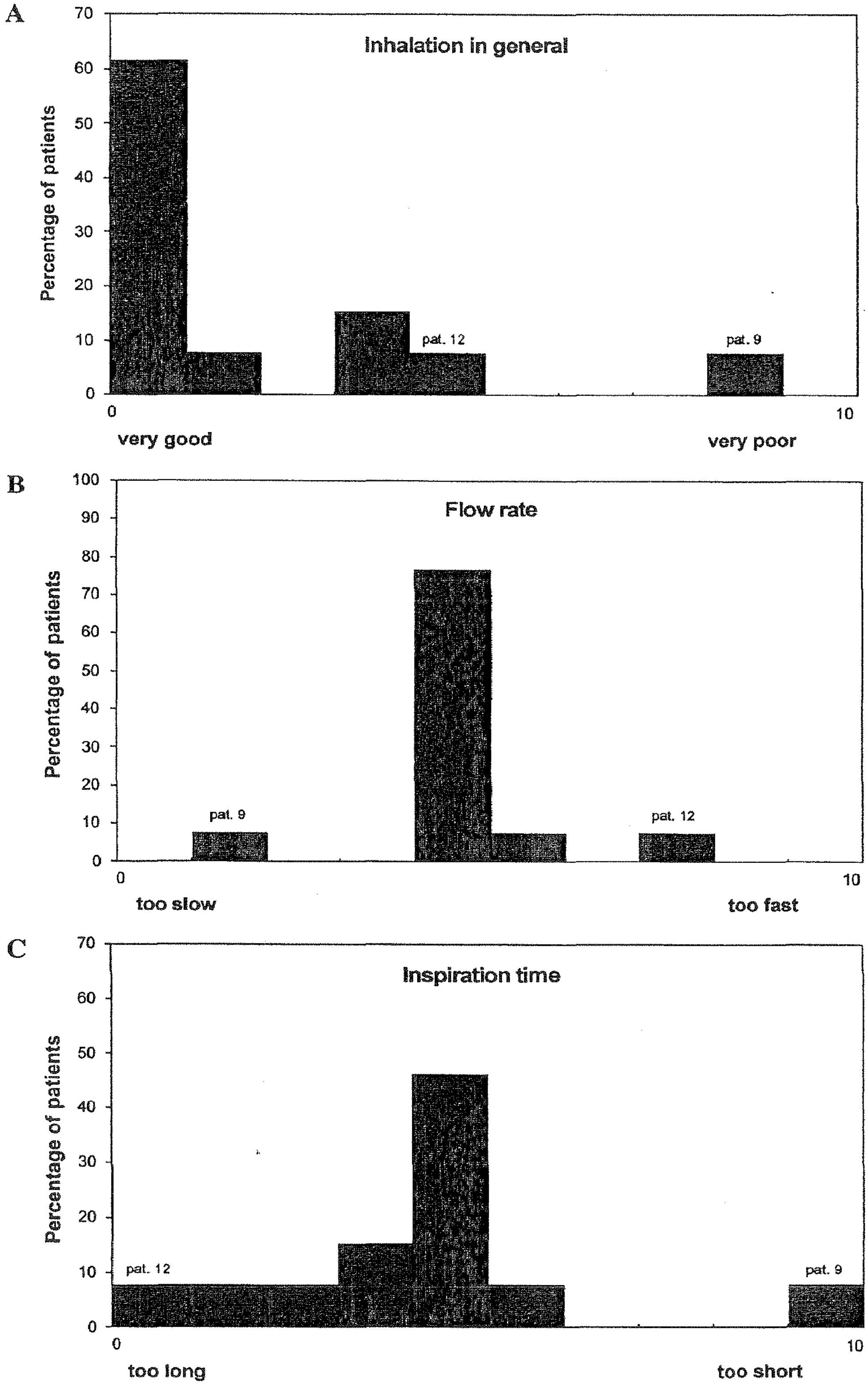

FIG. 4. Assessment of AKITA breath-controlled inhalation as given by 13 CF patients by means of a questionnaire. Frequency distribution of the scores (0–10) determined for the questions: (A) What is your general impression of inhalation with the AKITA? (B) What is your assessment of the speed of inhalation using AKITA? (C) What is your assessment of the time of inhalation for one breath using AKITA? The answers given by Patients 9 and 12 are marked, as they differed from those of the other patients.

parison of the function of these two devices suggests that the improved deposition noted for the AKITA device is attributable to a controlled breathing maneuver.

It has been repeatedly demonstrated that this inhalation with controlled breathing maneuver results in a higher and more peripheral lung deposition also in patients with a severe chronic obstructive lung disease (COPD).[4–6] Moreover, considering that the only patient with more severe lung disease in our CF group showed a substantial improvement in lung deposition, we believe that the AKITA device should be appropriate not only for CF patients with mild lung disease but also for those with more severe lung disease.

Even though the relative lung deposition (relative bioavailability) in intra-individual comparison can be clearly evaluated, only a rough estimate can be made for the percentage dose deposited into the lungs, from the urinary SCG excretion.[13] Assuming about half of the SCG dose to be excreted in urine, as determined in healthy volunteers after intravenous administration,[10,11,18] we estimate the average percentage of pulmonary deposition for AKITA controlled and manually triggered conventional inhalation (urinary excretion 2.2 mg and 1.6 mg) to be 22% and 16% of the nominal dose (20 mg), respectively. Adopting the same method, we noted in earlier investigations with CF patients that the average lung deposition was as low as 10% after inhalation using tidal breathing with the continuously operating Pari LC Plus nebulizer.[13,14] The lesser pulmonary deposition (10%) in those earlier investigations compared with the conventional inhalation in the present study (16%) could be accounted for by the different conditions of inhalation, that is, less deep inspiration, more output into the environment, and the larger droplet size of aerosol produced by the LC Plus nebulizer compared with the LC Star nebulizer.

Newman et al.,[3] using scintigraphy in healthy volunteers following inhalation with the LC Plus nebulizer, found the lung deposition to be of similar magnitude (13% of the nominal dose). Manually triggered operation of the nebulizer did not, as would have theoretically been expected, result in a significantly higher lung deposition compared with continuous operation. Healthy volunteers may not be adequately proficient to make efficient use of manual triggering. CF patients admitted to this study had regularly trained manual triggering and practiced to achieve an optimal breathing maneuver (deeply and slowly). Furthermore, throughout the test inhalations, they were observed by physiotherapists in order to ensure compliance with the instructions. By contrast, patients did not practice inhalation with the AKITA system until the day before the test inhalation. And yet, only two patients applying the conventional manually triggered inhalation achieved a good lung deposition (quantity and depth) comparable to that achieved with the AKITA system, that is, both an almost comparable amount of SCG in urine and a nearly similar SCG absorption half-life. Naturally, in patients lacking practice in manual triggering, one would expect the lung deposition by the AKITA system to be improved to an even greater extent compared with that noted in our study.

Following inhalation with the AKITA system, in a study conducted in adult patients,[6] the intersubject variability of total and peripheral deposition was noted to diminish substantially compared with the conventional inhalation, that is, the coefficient of variation decreased from 33% to 9% (total deposition) and from 56% to 16% (peripheral deposition). In our study, the coefficient of variation of the amount of SCG (representing lung deposition) was seen to drop only slightly, that is, from 36% to 27%. This could have been attributable to our study design, in which we exercised care to ensure that all the patients coped with the needs of manually triggered conventional inhalation and performed as required. The fairly high intersubject variability of lung deposition (amount of SCG) after AKITA inhalation, compared with the study conducted by Brand et al.[6] in adult patients (43–73 years), may have been due to the fact that our patients were much younger. The lung deposition is largely influenced by respiratory anatomy and physiology, which in our group of CF patients (8–20 years) additionally depended on age. Growth and geometric changes of the airways with increasing age entail a decrease in pharyngeal deposition and an increase in lung deposition, as demonstrated by Diot et al.[19] in CF patients (6–31 years). The statistically significant increase in the amount of SCG in urine (quantity of lung deposition) with an increase in FVC (L; coefficient of variation 43%) seen in this study could be interpreted in a similar way. This explanation is further supported by the fact that in our group of patients (8–20 years) the rise in FVC (L; range 1.1–5.5 L) with increasing age was highly significant ($r = 0.768$, $p = 0.002$).

In addition, the greater intersubject variability of the total SCG excretion (representing lung deposition), compared with the lung deposition determined by scintigraphy,[6] may have been the result of intersubject differences in renal excretion of SCG. However, Neale et al.,[11] studying healthy volunteers after intravenous administration of SCG, found a very small variation among the individuals in the ratio of SCG excreted in urine to that excreted in the bile (coefficient of variation about 5%). Yet, even if the inter-individual variability in renal excretion occurring in CF patients were assumed to be higher, this does not interfere with the primary message of our investigation, given that it was based on intra-individual comparisons of excreted SCG.

Eighty percent of the adult patients with slight bronchial asthma (22–61 years), filling in a questionnaire, assessed inhalation with the AKITA system as convenient.[17] We too noted that the children and adolescents with CF did not find it difficult to cope with the AKITA-controlled inhalation. Using the same questionnaire, 92% considered the inhalation in general as good or even very good. The breathing pattern defined by the device, that is, the individually adapted inhalation volume and the slow inhalation flow, were rated convenient by almost all of the patients. It was interesting to note that the two patients which gave a poorer assessment of inhalation with the device and considered the defined breathing parameters least adequate compared with the remaining patients exhibited a higher-than-average improvement of lung deposition (quantity and depth). The fact that AKITA was presented as a new device could have biased the patients' assessment of its convenience. Apart from that, however, supervision by the physiotherapist during the test inhalations verified that (i) the electronically breath-controlled inhalation was, in effect, very well tolerated by all the patients and (ii) no patient had to interrupt or abort the inhalation.

In conclusion, AKITA breath-controlled inhalation yields a greater and more peripheral lung deposition of SCG compared with manually triggered conventional inhalation with slow and deep inspiration, even in CF patients with several years of inhalation experience and supervised by a physiotherapist. Thus, our study verified that the efficiency of inhalation can be improved by electronic optimizing of the breathing maneuver.

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Lung deposition following electronically breath-controlled inhalation and manually triggered conventional inhalation in CF patients

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1.Introduction

The efficiency of inhalation is influenced by patients' inspiratory manoeuvre. An optimum breathing pattern can be achieved by electronically controlled inhalation using the AKITA aerosol delivery system.

However, it is still a question if an electronically guided inhalation can improve deposition in patients with long-time inhalation experience and who are assessed to perform a good breathing pattern.

2. Methods

Patients

- 13 CF patients, 8 - 20 years, (8 male / 5 female) *Pseudomonas aeruginosa* colonisation
- FEV_1 84 ± 18% pred. (38 - 109%)

Study design

- Measurement of lung function prior to each test inhalation (Pneumoscope®)
- Inhalation of 20 mg SCG (Intal® nebuliser solution)
- Randomised cross-over study
- Urine collection: 2 , 4 , 6 , 8 , and 12 h p.a.
- Washout period of 48 h before test inhalation
- Inhalations were supervised by a physiotherapist

Inhalation modes

I. Conventional manually triggered **LC Star**® nebuliser, manual interrupter, Parimaster® (Pari, Starnberg, Germany)

- Slow and deep breathing by patients

II. Electronically breath-controlled **AKITA**® + **LC Star**® nebuliser (Inamed, Gemünden, Germany)

- Optimum breathing pattern (Smart Card)
  - Inhalation flow rate 200 ml/s
  - Individualised inhalation volume (patient´s VC)
- Breath-actuated nebulisation

Determination of SCG in urine

- Solid-phase extraction (SPE)
- Reversed-phase HPLC, UV detection (Lichrograph®)

Sodium cromoglycate (SCG) as a marker substance

- Oral absorption less than 1%
- Pulmonary absorption nearly complete
- SCG is not metabolised
- Renal excretion 50%
- Amount of SCG in urine
  Quantity of lung deposition
- SCG absorption half-life
  More or less peripheral deposition

3. Results

Time of inhalation and residue

- Conventional inhalation (**LC Star)** was completed after 8.7± 2.4 min, and the electronically controlled inhalation (**AKITA+LC Star)** after 6.6 ± 0.9 min ($p=0.007$) (Fig. 1).
- The amounts of SCG retained in the nebulisers, however, were not significantly different (Fig. 1).

Cumulative excretion of SCG in urine

- After 6 hours, the excretion of SCG was almost complete: 92% and 95% of the total amount for the conventional (**LC Star**) and electronically controlled (**AKITA+LC Star**) inhalation, respectively (Fig. 2).

Comparison of total amount of SCG

- Following breath-controlled inhalation (**AKITA+LC Star**), the total amount of SCG excreted in urine was significantly greater than after conventional inhalation (**LC Star**) (2.22 mg ± 0.61 mg vs. 1.63 mg ± 0.59 mg, $p < 0.001$), being equivalent to an average increase of 46% (3-162%) (Fig. 3).

SCG absorption half-life (pharmacokinetics)

- Determination of the absorption half-life ($t_{1/2}$) is typically presented for patient No. 7 (Fig. 4). Inhaled SCG exhibits absorption limited kinetics i.e. absorption rate of SCG < elimination rate. [1] Slope of the line → rate of absorption (k_{abs}) .

$$t_{1/2} = \ln 2 / k_{abs}$$

Comparison of SCG absorption half -life

- The absorption half-life following breath-controlled inhalation (**AKITA+LC Star**) was significantly shorter when compared with conventional inhalation (**LC Star**) (78 ± 23 min vs. 107 ± 29 min; $p < 0.01$), being suggestive of a more peripheral deposition (Fig. 5).

(1) R. Richards et al., J. Pharmacol. Exp. Ther. 241 (1987),1028

4. Summary and Conclusion

- Electronically breath-controlled inhalation achieved a higher and more peripheral lung deposition of SCG compared with manually triggered conventional inhalation with slow and deep inspiration, even in CF patients with long-time inhalation experience.

Fig. 1

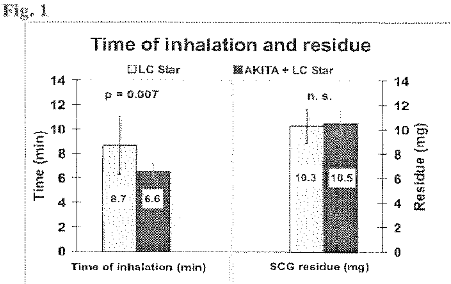

Fig. 2

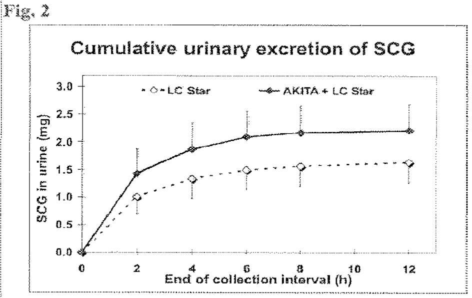

Fig. 3

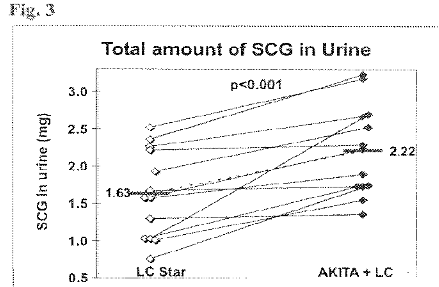

Fig. 4

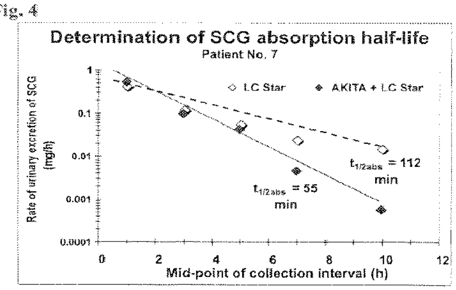

Fig. 5